

Response to treatment of congenital adrenal hyperplasia in infancy

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Abstract

Nine infants with congenital adrenal hyperplasia were started on replacement doses of hydrocortisone (20.6–32.6 mg/m²/day) without receiving a high dose for an initial period first. Plasma adrenal steroid concentrations fell to acceptable levels by 3 months of age. Adequate biochemical control was maintained and satisfactory growth achieved even though the mean dose of hydrocortisone had been reduced to 15 mg/m²/day by the age of 3 years. Inadvertent overtreatment and growth suppression in infants with congenital adrenal hyperplasia may be avoided by using replacement doses from the start, and by permitting the relative dose of hydrocortisone to fall as the body surface area increases during the first years of life.

dose of steroid during the intercurrent illnesses characteristic of infancy and early childhood can lead to adverse effects unless it is monitored closely.

In this paper we report a prospective study of longitudinal growth and changes in plasma adrenal steroid concentrations in nine infants with congenital adrenal hyperplasia. They received hydrocortisone after birth in replacement doses, adjusted during the subsequent 3 years of life according to frequent timed measurements of plasma adrenal steroid concentrations. The results indicate that an initial period of high doses of glucocorticoids is unnecessary; a subsequent maintenance dose of hydrocortisone that permits minimally raised concentrations of plasma adrenal steroids may be needed to prevent growth suppression in infancy and early childhood.

The treatment of congenital adrenal hyperplasia in infancy and childhood usually results in reduced adult height.¹ Inadvertent overtreatment with glucocorticoids (particularly during infancy) and failure of catch up growth despite subsequent reduction of the dose of steroids are important contributors.² Several aspects of conventional management have led to overtreatment. Treatment was started with high doses of glucocorticoid to achieve rapid control, the dose then being reduced to maintenance replacement doses. The early recommended doses of glucocorticoids, which were based on urinary steroid excretion rates, were excessive. Those calculated according to the known rate of endogenous cortisol production, provide a general framework for adequate treatment, but individual patients can vary in their requirements for glucocorticoid replacement.^{3,4} The use of urinary steroid excretion rates and single, random measurements of plasma adrenal androgen concentrations are not sensitive enough to detect glucocorticoid overdosage if there are no clinical signs.⁵ The practice of increasing the

Patients and methods

The diagnosis of congenital adrenal hyperplasia in nine patients (seven with classical salt wasting 21-hydroxylase deficiency, and two siblings with 11 β -hydroxylase deficiency) was established soon after birth (table). 21-Hydroxylase deficiency was confirmed by increased plasma 17OH-progesterone concentrations, which were measured in one or more samples collected before treatment was started. The diagnosis of 11 β -hydroxylase deficiency was based on raised plasma concentrations of 11-deoxycortisol and increased urinary excretion of its metabolite, tetrahydro-11-deoxycortisol. Plasma testosterone concentrations were also raised in the six patients in whom the steroid was measured before treatment.

Two patients (cases 5 and 7) each of whom had a salt losing crisis, initially required saline given intravenously and a single bolus dose of hydrocortisone. Oral glucocorticoid treatment was started within 1–47 days (mean 13) of presentation, and was given as hydrocortisone

Clinical details of infants with congenital adrenal hyperplasia and maximum steroid concentrations at diagnosis

Case No	Sex	Presentation	Age at diagnosis	Enzyme deficiency	Maximum 17OH-progesterone concentration (nmol/l)	Maximum testosterone concentration (nmol/l)
1	M	Prenatal diagnosis	16 weeks' gestation	21-hydroxylase	>380	>26.0
2	M	Failure to thrive	5 weeks	21-hydroxylase	>760	>26.0
3	M	Diarrhoea vomiting	2 weeks	21-hydroxylase	>380	Not measured
4	F	Ambiguous genitalia	2 weeks	21-hydroxylase	670	11.2
5	M	Failure to thrive	17 days	21-hydroxylase	1430	18.0
6	F	Ambiguous genitalia	1 day	21-hydroxylase	197	Not measured
7	M	Failure to thrive	1 month	21-hydroxylase	780	Not measured
8	F	Ambiguous genitalia	1 day	11 β -hydroxylase	1870*	22.0
9	F	Ambiguous genitalia	4 days	11 β -hydroxylase	>2000*	7.7

*=11-Deoxycortisol (nmol/l); >=concentrations above the upper limit of assay available at that time.

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Accepted 30 October 1989

in three divided doses, the total dose being 20.6–32.6 mg/m²/day (mean 25.7). Patients with 21-hydroxylase deficiency were also given fludrocortisone 0.1–0.15 mg/day.

Concentrations of testosterone, 17OH-progesterone, and 11-deoxycortisol were measured serially in blood samples collected between 0900–1100 at clinic visits every three months for up to three years after the start of treatment. Supine length (and later standing height) and weight were measured at each visit by a single trained observer. Growth velocity was calculated over six month intervals during the first year, and subsequently over periods of one year. Surface area was calculated from the height and weight according to standard nomograms.

Plasma concentrations of 17OH-progesterone,⁶ testosterone,⁷ and 11-deoxycortisol⁸ were measured using previously published methods.

Results

PLASMA 17OH-PROGESTERONE CONCENTRATIONS

The table and fig 1 show plasma 17OH-proges-

terone concentrations before and during the first month of treatment with hydrocortisone. The concentrations of 17OH-progesterone before treatment were high, a maximum of 1430 nmol/l being recorded. The concentrations of 17OH-progesterone in infants with 21-hydroxylase deficiency at some time before treatment were far higher than those found in normal or sick preterm infants, but values fluctuated from day to day to as low as 31 nmol/l.⁹ Those infants from whom several samples were taken during a single day showed no diurnal rhythm in 17OH-progesterone concentrations, but on one occasion there was a fall from 1430 to 273 nmol/l over a two hour period. 17OH-Progesterone concentrations in the two siblings with 11 β -hydroxylase deficiency were only slightly increased.

The pattern of plasma 17OH-progesterone concentrations during the first two years of life is shown in fig 2. By 3 months of age acceptable concentrations (median 84.1, interquartile range 11.3–90 nmol/l) of 17OH-progesterone had been achieved. There was a continued fall over the next two years without an increase in the daily dose of glucocorticoid.

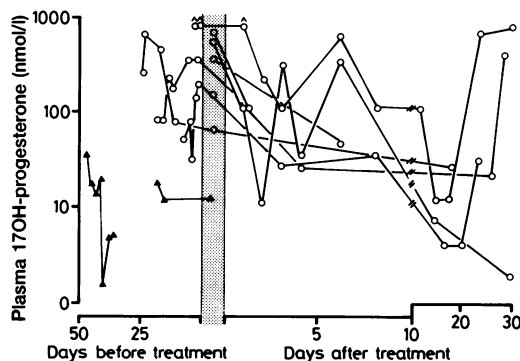


Figure 1 Plasma 17OH-progesterone concentrations in infants with congenital adrenal hyperplasia before and during first month of treatment with hydrocortisone. Shaded bar indicates start of treatment. (○=21-hydroxylase deficiency (n=7); ▲=11 β -hydroxylase deficiency (n=2)).

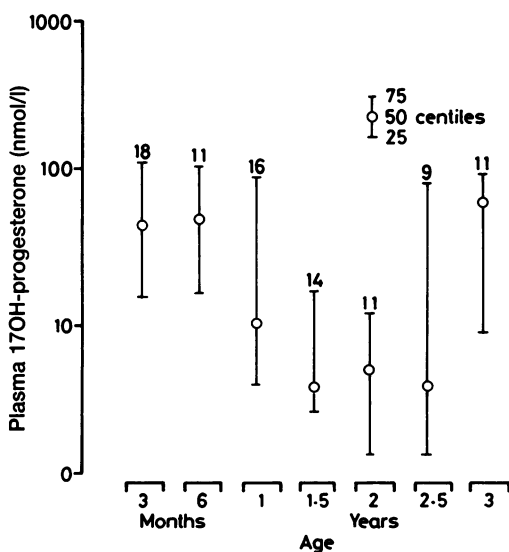


Figure 2 Plasma 17OH-progesterone concentrations achieved at various ages in infants with treated 21 hydroxylase deficiency (n=7). Centile values are derived from multiple measurements (number shown above bars) taken within one month of indicated age.

PLASMA TESTOSTERONE CONCENTRATIONS

Plasma testosterone concentrations were measured before treatment in six patients (table), and in both 21-hydroxylase deficiency and 11 β -hydroxylase deficiency they were considerably increased; they were within the normal range for adult men in all but one patient. Figure 3 shows the pattern of plasma testosterone concentrations during the early years of treatment. By the age of 3 months plasma testosterone concentrations had not yet come within the normal prepubertal range; those in male infants were slightly higher, consistent with the known increase in testicular testosterone production at this age.¹⁰

The plasma concentration of the specific marker for 11 β -hydroxylase deficiency, 11-deoxycortisol, was considerably increased in both siblings at diagnosis (table).¹¹ Concentrations of this steroid fell towards normal after three months of treatment (unpublished observations).

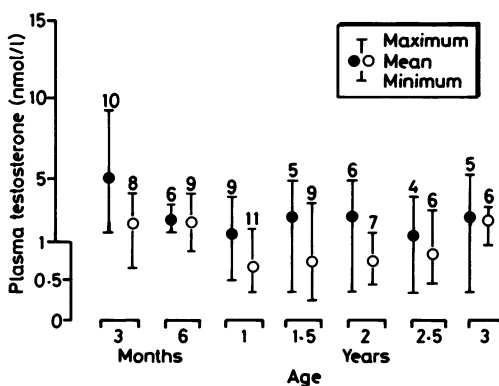


Figure 3 Plasma testosterone concentrations achieved at various ages in infants with treated congenital adrenal hyperplasia of all types (●=boys, n=5; ○=girls, n=4). Means and ranges are derived from multiple measurements (number shown above bars) taken within one month of indicated age.

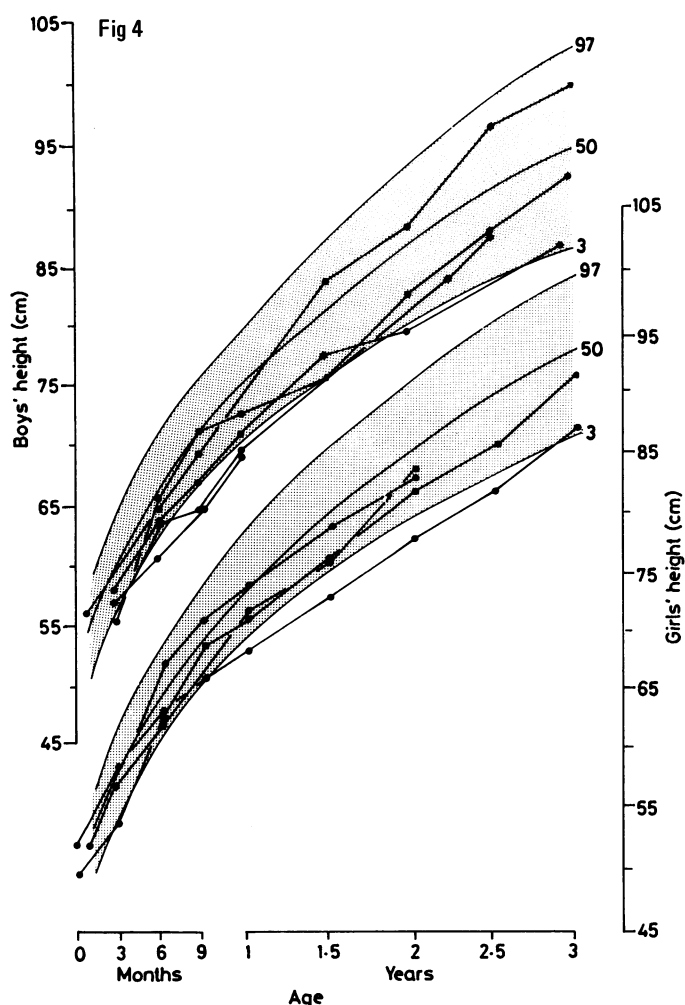


Figure 4 Height/length distance charts showing longitudinal growth data for nine infants (five boys, four girls) with treated congenital adrenal hyperplasia; 3, 50, and 97 indicate the respective centile lines.

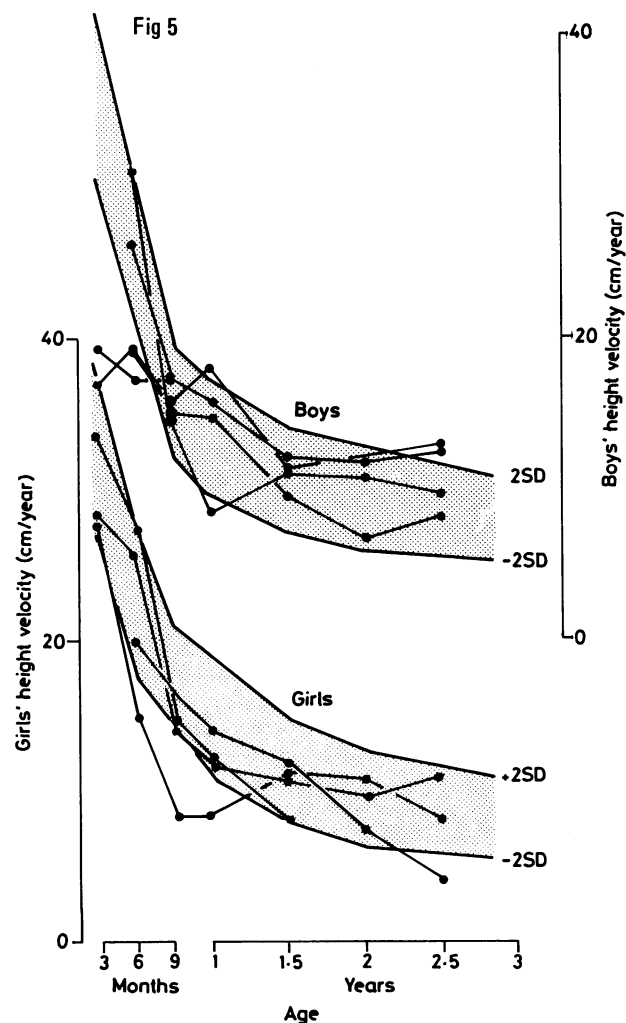


Figure 5 Growth velocity in nine infants with treated congenital adrenal hyperplasia (five boys, four girls). The shaded area encompasses the mean (2 SD) velocity data adapted from values provided by Tanner et al.¹³

GROWTH

The growth patterns during infancy and early childhood are shown in figs 4 and 5. Growth was generally normal; a few patients showed evidence of slower growth at 1 year, but then showed catch up growth as the dose of glucocorticoid was allowed to decrease in relation to increasing surface area.

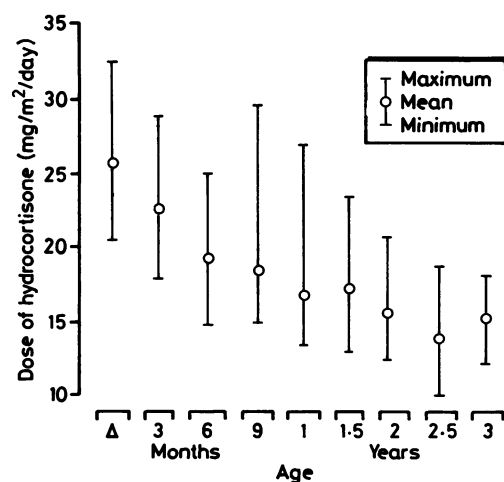


Figure 6 Doses of hydrocortisone achieved at various ages in nine infants with treated congenital adrenal hyperplasia; Δ indicates start of treatment.

TREATMENT WITH GLUCOCORTICIDS

The changes in the dose of hydrocortisone with increasing age of the patients is shown in fig 6. There was a gradual decline from the mean starting dose ($25.7 \text{ mg/m}^2/\text{day}$, range $20.1\text{--}32.6$) as a result of using a fixed prescribed dose of hydrocortisone as each patients' surface area increased with growth.

Discussion

Measurement of the plasma 17OH-progesterone concentration is widely accepted as a reliable test for the diagnosis of 21-hydroxylase deficiency congenital adrenal hyperplasia.⁴ Maximum 17OH-progesterone concentrations in this study were clearly high compared with those of normal newborn infants. Wide fluctuations, however, resulted in some 17OH-progesterone values falling within the ranges found in sick premature infants without congenital adrenal hyperplasia.⁹ As a precaution, multiple estimations of 17OH-progesterone concentrations may be needed when investigating suspected congenital adrenal hyperplasia in newborn infants. Glucocorticoid treatment can usually be delayed until samples have been collected; the ability to measure 17OH-progesterone concentrations in blood spots or saliva eases the

difficulty of collecting multiple blood samples from infants.⁴

The clinical hallmark of congenital adrenal hyperplasia caused by both 21-hydroxylase and 11 β -hydroxylase deficiencies is virilisation in an affected girl. Plasma testosterone concentrations in all six infants studied were increased, and reached the normal range for adult men in two baby girls. Despite the profound androgenic influence that had existed prenatally, there was no evidence of masculinisation of the male external genitalia at birth, yet—if they had been left untreated—signs of masculinisation would have occurred during the second year of post-natal life. There is no ready explanation for this apparent development related onset of androgen responsiveness of the male genitalia. It used to be normal practice to start treatment with large doses of glucocorticoid, often administered parenterally, in order to achieve rapid suppression of adrenal androgen production.

The results of this study suggest that initial high dose treatment is unnecessary. Oral hydrocortisone (and fludrocortisone where appropriate) in replacement doses alone (hydrocortisone dose: mean 25.7 mg/m²/day, range 20.6–32.6; fludrocortisone 0.1–0.15 mg/day) produced rapid and sustained falls in plasma adrenal steroid concentrations without adverse clinical effects. Initial doses of hydrocortisone were within the range usually used for treatment of congenital adrenal hyperplasia at this time of life.^{2,4} Doses larger than this lead to early growth suppression. The slower growth rate at 1 year in some infants in this study suggests that perhaps the dose of hydrocortisone used was still slightly excessive. There was a subsequent improvement in growth when the dose was allowed to fall in relation to the increase in body surface area. Adult height in congenital adrenal hyperplasia remains below normal.¹ Infancy and early childhood are critical periods of rapid growth. The use of high doses of glucocorticoid from the onset of treatment may contribute to irreversible suppression of growth during the period.

We recommend starting hydrocortisone in replacement doses (20–25 mg/m²/day), equivalent to about 5 mg/day. A typical regimen in early infancy would be hydrocortisone 1.25, 1.25, and 2.5 mg given at intervals of eight

hours. It is necessary to formulate hydrocortisone in solution to calculate these small doses accurately. During the next two years the dose may be allowed to fall to as little as 10 mg/m²/day while the body surface area increases. Overzealous attempts to achieve normal plasma concentrations of 17OH-progesterone should be avoided as this invariably leads to gross over-treatment.⁵ The use of steroid profiles may help in preventing inadvertent overdosage in older infants with an established diurnal rhythm for plasma 17OH-progesterone.

Close observation of linear growth remains a key measure of control during the period of rapid growth in early infancy,¹² together with the use of biochemical monitoring to help with the adjustment of doses of steroid in the short term.

MC Young was a joint Royal College of Physicians/British Paediatric Association Children Nationwide Fellow during the period of this study.

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